readable copies of the Sequence Listing, submitted in accordance with 37 CFR §1.821(a) through (c) and (e), respectively, are the same and include no new matter.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that making willful false statements and the like is punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Entry of the following amendment is respectfully requested.

Please amend the above-identified application as follows:

In the Specification:

Please replace the paragraph beginning at page 5, line 19, with the following rewritten paragraph:

In a still further aspect, the present invention provides a process of regulating the function of a nucleotide sequence that contains the sequence 5'-(GNN)n-3' (SEQ ID NO:123), where n is an integer from 1 to 6, the process comprising exposing the nucleotide sequence to an effective amount of a composition of this invention operatively linked to one or more transcription modulating factors. The 5'-(GNN)n-3' sequence can be found in the transcribed region or promotor region of the nucleotide or within an expressed sequence tag.

Please replace the paragraph beginning at page 10, line 20,

with the following rewritten paragraph:

From the combined selection and mutagenesis data it emerged that specific recognition of many nucleotides could be best accomplished using motifs, rather than a single amino acid. For example, the best specification of a 3' guanine was achieved using the combination of Arg-1, Ser1, and Asp2 (the RSD motif). By using Val5 and Arg6 to specify a 5' guanine, recognition of subsites GGG, GAG, GTG, and GCG could be accomplished using a common helix structure (SRSD-X-LVR) (SEQ ID NO:124) differing only in the position 3 residue (Lys3 for GGG, Asn3 for GAG, Glu3 for GTG, and Asp3 for GCG). Similarly, 3' thymine was specified using Thr-1, Ser1, and Gly2 in the final clones(the TSG motif). Further, a 3' cytosine could be specified using Asp-1, Pro1, and Gly2 (the DPG motif) except when the subsite was GCC; Pro1 was not tolerated by this subsite. Specification of a 3' adenine was with Gln-1, Ser1, Ser2 in two clones (QSS motif). Residues of positions 1 and 2 of the motifs were studied for each of the 3' bases and found to provide optimal specificity for a given 3' base as described here.

Please replace the paragraph beginning at page 13, line 24, with the following rewritten paragraph:

The data show that all possible GNN triplet sequences can be recognized with exquisite specificity by zinc finger domains. Optimized zinc finger domains can discriminate single base differences by greater than 100-fold loss in affinity. While many of the amino acids found in the optimized proteins at the key contact positions -1,3, and 6 are those that are consistent with a simple code of recognition, it has been discovered that optimal specific recognition is sensitive to the context in which

these residues are presented. Residues at positions 1,2, and 5 have been found to be critical for specific recognition. Further the data demonstrates for the first time that sequence motifs at positions -1,1, and 2 rather than the simple identity of the position 1 residue are required for highly specific recognition of the 3' base. These residues likely provide the proper stereochemical context for interactions of the helix both in terms of recognition of specific bases and in the exclusion of other bases, the net result being highly specific interactions. Broad utility of these domains would be realized if they were modular in both their interactions with DNA and other zinc finger domains. This could be achieved by working within the likely limitations imposed by target site overlap, namely that sequences of the 5'-$(GNN)_3$-3' type should be targeted. Ready recombination of the disclosed domains then allows for the creation of polydactyl proteins of defined specificity precluding the need to develop phage display libraries in their generation. These polydactyl proteins have been used to activate and repress transcription driven by the human *erbB-2* promoter in living cells. The family of zinc finger domains described herein is likely sufficient for the construction of 16^6 or 17 million novel proteins that bind the 5'-$(GNN)_6$-3' (SEQ ID NO:125) family of DNA sequences.

Please replace the paragraph beginning at page 20, line 13, with the following rewritten paragraph:

The *erbB-2* promoter therefore represents an interesting test case for the development of artificial transcriptional regulators. This promoter has been characterized in detail and has been shown to be relatively complex, containing both a TATA-

dependent and a TATA-independent transcriptional initiation site (Ishii, S., Imamoto, F., Yamanashi, Y., Toyoshima, K. & Yamamoto, T. (1987) *Proc. Natl. Acad. Sci. USA* **84**, 4374-4378). Whereas early studies showed that polydactyl proteins could act as transcriptional regulators that specifically activate or repress transcription, these proteins bound upstream of an artificial promoter to six tandem repeats of the proteins binding site (Liu, Q., Segal, D. J., Ghiara, J. B. & Barbas III, C. F. (1997) *Proc. Natl. Acad. Sci. USA* **94**, 5525-5530). Furthermore, this study utilized polydactyl proteins that were not modified in their binding specificity. Herein, we tested the efficacy of polydactyl proteins assembled from predefined building blocks to bind a single site in the native *erbB-2* promoter. Described above is the generation and characterization of a family of zinc finger domains that bind each of the 16 5'-GNN-3' DNA triplets. One reason we focused on the production of this family of recognition domains is that promoter regions of most organisms are relatively GC rich in their base content. Thus, if proteins recognizing 5'-$(GNN)_3$-3' sites could be readily assembled from this set of defined zinc finger domains, many genes could be rapidly and specifically targeted for regulation. A protein containing six zinc finger domains and recognizing 18 bp of DNA should be sufficient to define a single address within all known genomes. Examination of the *erbB-2* promoter region revealed two 5'-$(GNN)_3$-3'sites (SEQ ID NO:125) and one 5'-$(GNN)_3$-3' (SEQ ID NO:126) site. One of these sites, identified here as e2c, falls within the 5'-untranslated region of the *erbB-2* gene and was chosen as the target site for the generation of a gene-specific transcriptional switch. A BLAST sequence similarity search of the GenBank data base confirmed that this sequence is unique to *erbB-2*. The position of the e2c target sequence, downstream and in the

vicinity of the two major transcription initiation sites, allowed for the examination of repression through inhibition of either transcription initiation or elongation. An interesting feature of the e2c target site is that it is found within a short stretch of sequence that is conserved between human, rat, and mouse *erbB-2* genes (White, M. R.-A. & Hung, M.-C. (1992) *Oncogene* **7**, 677-683). Thus, targeting of this site would allow for the study of this strategy in animal models prior to its application to human disease.

Please replace the paragraph beginning at page 21, line 20, with the following rewritten paragraph:

The general utility of two different strategies for generating three-finger proteins recognizing 9 bp of DNA sequence was investigated. Each strategy was based on the modular nature of the zinc finger domain, and takes advantage of a family of zinc finger domains recognizing triplets of the 5′-GNN-3′. Two three-finger proteins recognizing halfsites (HS) 1 and 2 of the 5′-(GNN)$_2$-3′ (SEQ ID NO:125) *erbB-2* target site e2c were generated in the first strategy by fusing the pre-defined finger 2 (F2) domain variants together using a PCR assembly strategy. To examine the generality of this approach, three additional three-finger proteins recognizing sequences of the 5′-(GNN)$_2$-3′ type, were prepared using the same approach. Purified zinc finger proteins were prepared as fusions with the maltose binding protein (MBP). ELISA analysis revealed that serially connected F2 proteins were able to act in concert to specifically recognize the desired 9-bp DNA target sequences. Each of the 5 proteins shown was able to discriminate between target and non-target 5′-(GNN)$_2$-3′ sequence.